IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Toshihiro SHIMIZU et al. :

Serial No. 09/403,429 : Group Art Unit 1615

Filed on October 20, 1999 : Examiner: TRAN, Susan T.

For: RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of
Patents and Trademarks,
Washington, D.C. 20231

Sirs:

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd. (now, Takeda Pharmaceutical Company Limited), Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Production Division of said company;

That I have been appointed a Research Head of Pharmaceutical Technology Research & Development Laboratories in said Pharmaceutical Production Division since 2004;

That I was awarded a Ph. D in Formulation Study of Lansoprazole Fast-disintegrating Tablets containing Enteric Coated Microgranules from Kyushu University in March, 2005;

That I am a member of the Pharmaceutical Society of Japan, and have published, with other research workers, a number of reports on scientific studies, among others, including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)

2. Shimizu T., Kameoka N., Ikl H., Tabata T., Hamaguchi N., Igari Y., *Chem.*

Pharm. Bull., 51, 1029-1035 (2003)

3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003);

That I am one of the co-inventors of the above-identified U.S. Patent Application Serial No. 09/403,429 filed on October 20, 1999;

That the following Experiments were conducted by myself and under my supervision and control:

Experiments

Experiment 1

Purpose

The tablet shown in Example 2 of Depui et al. (US 6,365,184) was reproduced, and disintegration time and oral disintegration time were measured. As L-HPC, L-HPC LH-32 (hydroxypropoxyl group content: 7.0-9.9%) was used. Based on my knowledge and experience, I consider myself to be familiar with the materials that were commercially available for pharmaceutical formulations before the priority date of the present application (July 28, 1998). I believe that the L-HPC LH32 material would correspond to the material having the lowest hydroxypropoxyl group content that was commercially available, whether from Shin-Etsu or any other source, before the priority date of the present application (July 28, 1998).

Method

Enteric coated granules were produced at the mixing ratio of the enteric coated granules of Example 2 of Depui et al. (US 6,365,184) and using lansoprazole instead of omeprazole (Preparation A).

The formulations of US 6,365,184 (Example 2) and Preparation A are shown below.

1. Production of enteric coated granules
1.1. Active compound layer

Lansoprazole, magnesium carbonate, polysorbate 80 and hydroxypropyl methylcellulose were dissolved and suspended in purified water to give a suspension. Using a rotating fluidized-bed granulator, Nonpareil cores (Nonpareil 101 (24-32M)) were coated by spraying the suspension.

Table 1 Formulation of core and active compound layer

	Material	US6,365,184 (g)	Preparation A (g)
Core	Nonpareil cores	150	150
Active compound layer	S-omeprazole magnesium	120	-
	Lansoprazole	-	100
	Magnesium carbonate	-	20
	Polysorbate 80	2.4	2.4
	Hydroxypropyl methylcellulose	18	18
	Purified water	562	562
	Subtotal (solid ingredients)	140.4	140.4
		702.4	702.4
	Total	290.4	290.4

1.2. Separating layer

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water to give a separating layer suspension. Using a rotating fluidized-bed granulator, the core material obtained in above-mentioned 1.1 was coated by spraying the separating layer suspension and was dried.

Table 2 Formulation of separating layer

	Material	US6,365,184 (g)	Preparation A (g)
Core material	Core material	200	200
Separating layer	Hydroxypropyl cellulose	30	30
	Talc	51.4	51.4
	Magnesium stearate	4.3	4.3
	Purified water	600	600
	Subtotal (solid ingredients)	85.7	85.7
		685.7	685.7
	Total	285.7	285.7

1.3. Enteric coating layer

Polysorbate 80 was dissolved in purified water, and the mixture was heated to 70°C. Mono- and diglycerides were added, and the mixture was dispersed using a dispersing apparatus, and then cooled to room temperature. To this dispersion were added triethyl citrate and methacrylic acid copolymer 30% suspension, and they were mixed to give an enteric coating suspension.

Using a rotating fluidized-bed granulator, the pellets with separating layer obtained in above-mentioned 1.2 were coated by spraying the enteric coating suspension.

kneaded and dried in a shelf dryer at 60°C for 5 hr. The obtained granules were sized using a 1000 μm standard sieve.

Table 5 Formulation of NSAID Granules

Material	US6,365,184 (g)	Preparation A (g)
Naproxen	250	250
Microcrystalline cellulose	150	150
L-HPC LH-32	40	40
Polyvinylpyrrolidone K-90	5	5
Purified water	250	250
Total (solid ingredients)	445	445

3. Mixing and tableting

The over-coated pellets comprising lansoprazole and NSAID Granules were mixed 50 times in a bag. Using Shimazu universal testing machine (UH-10A) with a 11 mmφ flat punch, the mixed powder (500 mg) was tableted at a compression force of 9 KN/punch.

Table 6 Formulation of mixed powder

Material	US6,365,184 (g)	Preparation A (g)
Over-coated pellets comprising lansoprazole	55	55
NSAID Granules	445	445
Total	500	500

4. Property of tablet

The hardness, disintegration time and oral disintegration time of the tablet were measured.

Hardness: Hardness of each of 3 tablets was measured using Tablet tester 60 (Schleuniger) and mean value was calculated.

Disintegration time: The measurement was carried out according to the disintegration test method of EP (European Pharmacopoeia) using purified water as a test solution.

Oral disintegration time: The measurement was carried out in three healthy human subjects. After the mouth was rinsed with water, one tablet was held in the mouth until the tablet disintegrated without chewing. The disintegration time was recorded.

Results

The results of the measurements are shown in Table 7. Securing the equivalent hardness as in Example 2 of Depui et al. (US 6,365,184), the disintegration time and oral disintegration time were measured. In the disintegration test according to EP, the tablet was disintegrated in 30 sec, showing rapid disintegration property. As for the oral disintegration time, however, only about half of the tablet was found to have been disintegrated after staying in the mouth for 5 min.

Table 7 Results of measurements

	Example 2 of US 6,365,184 (reported)	Preparation A
Hardness (mean)	9.4 kP	9.7 kP
Disintegration time	15-30 sec	30-30 sec
Oral disintegration time	---	The tablet was not disintegrated in 5 min, too sticky and spit out due to uncomfortable feeling.

Experiment 2

Purpose

The disintegration time and oral disintegration time of the combination of Depui et al. (US 6,365,184) and Khankari et al. (US 6,024,981) (tablet of the formulation of Example 2 of Depui added with mannitol) were measured. As L-HPC, L-HPC LH-32 (hydroxypropoxyl group content: 7.0-9.9%) having the lowest hydroxypropoxyl group content, which was commercially available before the priority date of the present application (July 28, 1998), was used.

Method

Enteric coated granules were produced at the mixing ratio of the enteric coated granules of Example 2 of Depui et al. (US 6,365,184) and using lansoprazole instead of omeprazole. Furthermore, mannitol was added as an exipient (Preparation B).

The formulations of US 6,365,184 (Example 2) and Preparation B are shown below.

1. Production of enteric coated granules
1.1. Active compound layer

Lansoprazole, magnesium carbonate, polysorbate 80 and hydroxypropyl methylcellulose were dissolved and suspended in purified water to give a suspenstion.

Using a rotating fluidized-bed granulator, Nonpareil cores (Nonpareil 101 (24-32M)) were coated by spraying the suspension.

Table 8 Formulation of core and active compound layer

	Material	US6,365,184 (g)	Preparation B (g)
Core	Nonpareil cores	150	150
Active compound layer	S-omeprazole magnesium	120	-
	Lansoprazole	-	100
	Magnesium carbonate	-	20
	Polysorbate 80	2.4	2.4
	Hydroxypropyl methylcellulose	18	18
	Purified water	562	562
	Subtotal (solid ingredients)	140.4	140.4
		702.4	702.4
	Total	290.4	290.4

1.2. Separating layer

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water to give a separating layer suspension. Using a rotating fluidized-bed granulator, the core material obtained in above-mentioned 1.1 was coated by spraying the separating layer suspension and was dried.

Table 9 Formulation of separating layer

	Material	US6,365,184 (g)	Preparation B (g)
Core material	Core material	200	200
Separating layer	Hydroxypropyl cellulose	30	30
	Talc	51.4	51.4
	Magnesium stearate	4.3	4.3
	Purified water	600	600
	Subtotal (solid ingredients)	85.7	85.7
		685.7	685.7
	Total	285.7	285.7

1.3. Enteric coating layer

Polysorbate 80 was dissolved in purified water, and the mixture was heated to 70°C. Mono- and diglycerides were added, and the mixture was dispersed using a dispersing apparatus, and then cooled to room temperature. To this dispersion were added triethyl citrate and methacrylic acid copolymer 30% suspension, and they were mixed to give an enteric coating suspension.

Using a rotating fluidized-bed granulator, the pellets with separating layer obtained in above-mentioned 1.2 were coated by spraying the enteric coating suspension.

Table 10 Formulation of enteric coating layer

	Material	US6,365,184 (g)	Preparation B (g)
Pellets with separating layer	Pellets with separating layer	250	250
Enteric coating layer	Methacrylic acid copolymer 30% suspension (as solid ingredient)	333.7 (100.1)	333.7 (100.1)
	Triethyl citrate	30	30
	Mono-and diglycerides	5	5
	Polysorbate 80	0.5	0.5
	Purified water	195.8	195.8
	Subtotal (solid ingredients)	135.6 565	135.6 565
	Total	385.6	385.6

1.4. Over-coating layer

Carboxymethylcellulose sodium was dissolved in purified water to give an over-coating solution. Using a rotating fluidized-bed granulator, the enteric coating layered pellets obtained in above-mentioned 1.3 were coated by spraying the over-coating solution and was dried.

Table 11 Formulation of over-coating layer

	Material	US6,365,184 (g)	Preparation B (g)
Enteric coating layered pellets	Enteric coating layered pellets	371	371
Over-coating layer	Carboxymethylcellulose sodium	5	5
	Purified water	191	191
	Subtotal (solid ingredient)	5 196	5 196
	Total	376	376

2. NSAID Granules

Polyvinylpyrrolidone K-90 was dissolved in purified water to give a binding

solution. Using a vertical granulator (FM-VG-10), naproxen, mannitol, microcrystalline cellulose and L-HPC LH-32 were mixed. The binding solution was added and the mixture was kneaded and dried in a shelf dryer at 60°C for 5 hr. The obtained granules were sized using a 1000 μm standard sieve.

Table 12 Formulation of NSAID Granules

Material	US6,365,184 (g)	Preparation B (g)
Naproxen	250	250
Mannitol	-	300
Microcrystalline cellulose	150	150
L-HPC LH-32	40	40
Polyvinylpyrrolidone K-90	5	5
Purified water	250	250
Total (solid ingredients)	445	745

3. Mixing and tableting

The over-coated pellets comprising lansoprazole and NSAID Granules were mixed 50 times in a bag. Using Shimazu universal testing machine (UH-10A) with a 11 mmϕ flat punch, the mixed powder (500 mg) was tableted at a compression force of 9 KN/punch.

Table 13 Formulation of mixed powder

Material	US6,365,184 (g)	Preparation B (g)
Over-coated pellets comprising lansoprazole	55	55
NSAID Granules	445	445
Total	500	500

4. Property of tablet

The hardness, disintegration time and oral disintegration time of the tablet were measured.

Hardness: Hardness of each of 3 tablets was measured using Tablet tester 60 (Schleuniger) and mean value was calculated.

Disintegration time: The measurement was carried out according to the disintegration test method of EP (European Pharmacopoeia) using purified water as a test solution.

Oral disintegration time: The measurement was carried out in three healthy human subjects. After the mouth was rinsed with water, one tablet was held in the mouth until

October 2003 Chem. Pharm. Bull. 51(10) 1121—1127 (2003) 1121

Formulation Study for Lansoprazole Fast-disintegrating Tablet. III. Design of Rapidly Disintegrating Tablets

Toshihiro SHIMOZU,* Masae SUGAYA, Yoshinori NAKANO, Daisuke IZUTSU, Yoshio MIZUKAMI, Kazuhiro OKOCHI, Tetsuro TABATA, Naoto HAMAGUCHI, and Yasutaka IGARI

Pharmaceutical Development Laboratories, Pharmaceutical Production Division, Takeda Chemical Industries, Ltd.: 2–17–85 Juso-honmachi, Yodogawa-ku, Osaka 532–8686, Japan. Received February 24, 2003; accepted July 4, 2003

Lansoprazole fast-disintegrating tablets (LFDT) are a patient-friendly formulation that rapidly disintegrates in the mouth. LFDT consist of enteric-coated microgranules (mean particle size, approximately 300 μm) and inactive granules. In the design of the inactive granules, mannitol was used as a basic excipient. Microcrystalline cellulose, low-substituted hydroxypropyl cellulose (L-HPC), and crospovidone were used as binders and disintegrants. A new grade of L-HPC (L-HPC-33), with a hydroxypropoxy group content of 5.0—6.9%, was developed and it has no rough texture due to a decrease in water absorption. It was clarified that L-HPC-33 could be useful as a binder and disintegrant in rapidly disintegrating tablets. LFDT contain enteric-coated microgranules in tablet form. The enteric-coated microgranule content in LFDT affect qualities such as tensile strength, disintegration time in the mouth, and dissolution behavior in the acid stage and in the buffer stage of LFDT. The 47.4% content of the enteric-coated microgranules was selected to give sufficient tensile strength (not less than 30 N/cm²), rapid disintegration time in the mouth (not more than 30 s), and dissolution behavior in the acid stage and buffer stage similar to current lansoprazole capsules. Compression force affected the tensile strength and the disintegration time in the mouth, but did not affect the dissolution behavior in the acid and buffer stages.

Key words rapidly disintegrating tablets; roughness; L-HPC; compression force; dissolution

Tablets that disintegrate rapidly in the mouth are convenient for patients who have difficulty in swallowing conventional oral dosage forms. Although various manufacturing technologies such as tablet molding,[1,2] freeze-drying,[3—9] spray-drying,[8—11] disintegrant addition,[12—16] sublimation,[17] and sugar-based excipients[18] have been studied, rapidly disintegrating tablets that are superior in both pharmaceutical function, for example, sustained-release dosage forms and enteric dosage forms, and in ease of swallowing have rarely been reported. Lansoprazole, a substituted benzimidazole, is a highly specific inhibitor of gastric (H^++K^+)-ATPase.[19,20] Since lansoprazole is unstable under acidic conditions, it is necessary to design enteric dosage forms that can protect against degradation in the stomach. Lansoprazole is marketed as a capsule containing enteric-coated granules, but some patients may find capsules difficult to swallow due to their size. Therefore it has been thought necessary to develop a patient-friendly enteric dosage form that is easy to swallow.

The purpose of this study was to develop a new formulation of lansoprazole, lansoprazole fast-disintegrating tablets (LFDT), which are rapidly disintegrating tablets that are easy to swallow as well as an enteric dosage form, with a simple manufacturing method using a conventional tablet press. LFDT consist of enteric-coated microgranules and inactive granules. In our previous studies,[21,22] we reported the design of multifunctional enteric-coated microgranules with improved oral acceptance, sufficient flexibility of the enteric layers against compression, and improved stability of lansoprazole. In the design of the inactive granules, it was necessary to find a suitable binder with excellent compactibility and a suitable rapid disintegrant in saliva. We formulated the inactive granules using four excipients, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose (L-HPC), and crospovidone. Mannitol was used as the basic excipient because it has a sweet taste and leaves a cooling sensation in the mouth. Microcrystalline cellulose was used as a binder as it has high water absorbency, and tablets containing microcrystalline cellulose are characterized by short disintegration time, high hardness, and low friability. L-HPC was used as a binder and disintegrant because it has different properties as a binder and disintegrant by selecting particle size and substitution level (hydroxypropoxy group content). Crospovidone was used as a disintegrant as it rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gel. However, the rapidly disintegrating tablets comprised of a large amount of water-insoluble excipients may feel rough. We evaluated the effects of hydroxypropoxy group content in L-HPC on the sensation of LFDT and clarified the effects of compression on the properties of LFDT, such as the tensile strength, disintegration time in the mouth, dissolved percentage in the acid stage, and dissolution profiles in the buffer stage.

Experimental

Materials Lansoprazole was synthesized at Takeda Chemical Industries, Ltd. Commercial lansoprazole capsules were obtained in-house at Takeda Chemical Industries, Ltd.

Lactose monohydrate-microcrystalline cellulose spheres (Nonpareil 105T, mean particle size 150—180 μm) and L-HPC (hydroxypropoxy groups: L-HPC-33, 5.0—6.9%; L-HPC-30, 13.0—16.0%) were kindly supplied by Freund Industrial Co., Ltd., and Shin-Etsu Chemical Co., Ltd., respectively. Methacrylic acid copolymer dispersion (Eudragit® L30D-55) and ethyl acrylate–methyl methacrylate copolymer dispersion (Eudragit® NE30D) were purchased from Röhm GmbH. L-HPC (hydroxypropoxy groups: L-HPC-32, 7.0—9.9%; L-HPC-31, 10.0—12.9%) and hydroxypropyl methylcellulose 2910 (TC-5 RW) were purchased from Shin-Etsu Chemical Co., Ltd. Mannitol and polysorbate 80 were purchased from Merck Japan Ltd. Magnesium carbonate (Tomita Pharmaceutical Co., Ltd.), hydroxypropyl cellulose (HPC-SSL, Nippon Soda Co., Ltd.), talc (Matsumura Industrial Co., Ltd.), glyceryl monostearate (P-100, Riken Vitamin Co., Ltd.), macrogol 6000 (Sanyo Chemical Industries, Ltd.), triethyl citrate (Citroflex 2, Morimura Bros., Inc.), microcrystalline cellulose (Ceolus KG-801, Asahi Chemical Industry Co., Ltd.), crospovidone (Polyplasdone XL-10, ISP Japan Ltd.), colloidal silicon dioxide (Nikkei Chemicals Co., Ltd.), and magnesium stearate (Taihei

* To whom correspondence should be addressed. e-mail: Shimizu_Toshihiro@takeda.co.jp

Chemical Industrial Co., Ltd.) were purchased. Yellow ferric oxide (Anstead International Co., Ltd.) and red ferric oxide (BASF Japan Ltd.) were used as the pigments. All other excipients used in the dosage forms are specified in the Japanese Pharmacopoeia (JP) and Japanese Pharmaceutical Excipients.

Viscosity of L-HPC Suspension Sixty grams of accurately weighed L-HPC was transferred to 600 ml of purified water in dissolution apparatus 2 (paddle) and suspended at 200 rpm for 30 min. The purified water was previously kept at 25±0.5 °C. Viscosity of the suspension was measured using a digital viscometer (Type DVL-BII, Tokimec Inc., Japan). The viscosity was measured three times.

Sensory Evaluation of Roughness of L-HPC Sensory tests of the threshold value of the roughness of L-HPC-31 were carried out in 6 volunteers. After the mouth was rinsed with purified water, L-HPC-31 10—40 mg was held in the mouth for ca. 10 s and spat out, and the mouth was rinsed again. Results showed the roughness threshold weight to be 20 mg. Sensory evaluation of the roughness of different L-HPC 30 mg was then carried out and the roughness level recorded. A numerical scale was used with the following values: 0, no roughness; 1, slight roughness; and 2, roughness.

Sensory Evaluation of Disintegration and Roughness of Tablets Flat-faced direct-compression tablets 300 mg in weight and 10 mm in diameter were prepared using a rotary tablet press (Correct 12 HUK, Kikusui Seisakusho, Ltd., Japan) at compression force of 9.8 kN/cm² and compression speed of 20 rpm, as shown in Table 1.

Sensory tests of roughness and disintegration of tablets were carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth for 60 s and then spat out, and the mouth was rinsed again. The roughness level and the dissolution level were recorded. A numerical scale was used with the following values: 0, no roughness; 1, slight roughness; and 2, roughness; and 0, rapidly; 1, moderately; 2, slowly, and 3, not disintegrated.

Preparation of LFDT LFDT consist of enteric-coated microgranules (mean particle size, approximately 300 μm) containing lansoprazole and inactive granules. Previously we reported the design of the enteric-coated microgranules.[21,22] We had to resolve the three issues of damage to the enteric layer during the compression process, the unpleasant bitter taste of triethyl citrate, and the poor stability of lansoprazole in the enteric-coated microgranules. Finally we developed enteric-coated microgranules comprising seven layers: 1) core, 2) active compound layer, 3) intermediate layer (stabilization of lansoprazole), 4) first enteric layer (stabilization of lansoprazole), 5) second enteric layer (reduction of damage to the enteric layer during the compression process), 6) third enteric layer (masking the unpleasant bitter taste), and 7) overcoating layer (preventing agglomeration of enteric-coated microgranules during the drying process) with improved oral acceptance, sufficient flexibility of the enteric layers against compression, and improved stability of lansoprazole.

Coating of Active Compound Layer and Intermediate Layer Table 2 presents the formulation in the preparation of lansoprazole-coated microgranules. An active compound suspension consisting of lansoprazole, magnesium carbonate, L-HPC-32, hydroxypropyl cellulose, and purified water was prepared by stirring. An intermediate suspension consisting of hydroxypropyl methylcellulose 2910, L-HPC-32, talc, titanium dioxide, mannitol, and purified water was prepared by stirring. Lactose monohydrate-microcrystalline cellulose spheres were coated consecutively by spraying the active compound suspension and the intermediate suspension in a rotating fluidized-bed granulator (Multiplex MP-10, Powrex Co., Ltd., Japan). Table 3 lists the operating conditions for coating. The above granules were dried in the rotating fluidized-bed granulator.

Coating of the Enteric Layer Table 2 presents the formulations in the preparation of the enteric layer. A glyceryl monostearate emulsion consisting of glyceryl monostearate, polysorbate 80, pigment, and purified water was prepared by homogeneous dispersion in a dispersing machine. An enteric-coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate–methyl methacrylate copolymer dispersion, glyceryl monostearate emulsion, macrogol 6000, citric acid, and purified water was prepared by stirring. An enteric-coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate–methyl methacrylate copolymer dispersion, glyceryl monostearate emulsion, triethyl citrate, citric acid, and purified water was prepared by stirring. An overcoating solution consisting of mannitol and purified water was prepared by stirring.

Lansoprazole-coated microgranules were coated consecutively by spraying two-thirds part of the first enteric coating suspension, the second enteric coating suspension, the remaining one-third of the first enteric coating suspension, and the overcoating solution in the rotating fluidized-bed granulator. Table 3 lists the operating conditions for coating. The above granules were then dried in the rotating fluidized-bed granulator.

Table 1. Formulation of Tablets

Erythritol		239.1 mg
Low-substituted hydroxypropyl cellulose		60.0 mg
Magnesium stearate		0.9 mg
	Total	300.0 mg

Preparation of LFDT Table 4 presents the formulations in the preparation of the inactive granules. A binder solution consisting of mannitol, citric acid, and purified water was prepared by stirring. Mannitol, L-HPC-33, microcrystalline cellulose, crospovidone, and aspartame were granulated by spraying the binder solution into a fluid-bed granulator (FD-3S, Powrex Co., Ltd., Japan). Table 5 lists the operating conditions for the granulation. The above granules were then dried in the fluid-bed granulator.

The enteric-coated microgranules, the inactive granules, flavoring, and magnesium stearate were mixed in the weight ratios shown in Table 4. The mixed granules were compressed with a rotary tablet press (Correct 12HUK, Kikusui Seisakusho, Ltd., Japan). Tablets 420, 570, and 720 mg in weight, and 12 mm in diameter were prepared at 30 rpm compression speed and 20 kN/cm² compression force. Tablets 570 mg in weight and 12 mm in diameter were prepared at 30 rpm compression speed and at three different compression forces (20, 25, and 30 kN/cm²).

Tablet Tensile Strength The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a tablet hardness tester (Toyama Sangyo Co., Ltd., Japan). The test was performed in 10 runs and the average was calculated. Tensile strength for crushing (T) was calculated using the following equation: $T=2F/(\pi dt)$, where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Disintegration Time in the Mouth Measurements of disintegration time in the mouth were carried out in 6 volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth until the tablet disintegrated without chewing and then spat out, and the mouth was rinsed again. The disintegration time was recorded.

Dissolution Testing Dissolution tests were performed in accordance with USP 24 Dissolution ⟨711⟩ and Drug Release ⟨724⟩ using apparatus 2 (paddle). The paddle was driven at 75 rpm. The test comprised the following two stages.

Acid Stage: Five hundred milliliters of 0.1 N HCl was used as the dissolution medium. The dissolution percentage after 60 min was measured. The amount of lansoprazole dissolved in the dissolution medium was determined by spectrophotometry (wavelength: 306 nm) after filtration through a membrane filter (0.45 μm, Acrodisc LC; PVDF, Gelman, P/N 44060).

Buffer Stage: Immediately after the test medium was withdrawn from the acid stage, 425 ml of the buffer concentrate (pH 11.4) was added and 900 ml of phosphate buffer containing 5 mM sodium dodecyl sulfate (pH 6.75—6.85) was obtained. The medium samples were collected at 15, 30, 45, and 60 min. The amount of lansoprazole dissolved in the dissolution medium was determined by spectrophotometry (wavelength: 286 nm) after filtration through a membrane filter (0.45 μm, Acrodisc LC; PVDF, Gelman, P/N 4408).

Results and Discussion

Effect of Hydroxypropoxy Group Content in L-HPC on the Qualities of LFDT Watanabe *et al.*[20] reported that tablets prepared with microcrystalline cellulose and L-HPC rapidly disintegrated in saliva. However, it was indicated that patients sometimes sensed roughness in the mouth due to the incomplete solubilization of this type of tablet in saliva.[17] In the design of the inactive granules, microcrystalline cellulose, L-HPC, and crospovidone were used as binders and disintegrants. These water-insoluble excipients have a very rough texture and it was thought that their particle size and the water absorption properties might result in the rough texture. Water-insoluble excipients with small particle size are smoother than water-insoluble excipients with large particle size. Ishikawa *et al.*[10] noted the relationship between the particle size of microcrystalline cellulose and rough texture and

Table 2. Formulation of Enteric-Coated Microgranules

Core	Lactose monohydrate-microcrystalline cellulose spheres		30.0 mg
Active compound layer	Lansoprazole		30.0 mg
	Magnesium carbonate		10.0 mg
	Low-substituted hydroxypropyl cellulose (L-HPC-32)		5.0 mg
	Hydroxypropyl cellulose		10.0 mg
	Purified water[a]		128 μl
Intermediate layer	Hydroxypropyl methylcellulose 2910		7.0 mg
	Low-substituted hydroxypropyl cellulose (L-HPC-32)		5.0 mg
	Talc		3.0 mg
	Titanium dioxide		3.0 mg
	Mannitol		7.0 mg
	Purified water[a]		100 μl
Enteric layer 1	Methacrylic acid copolymer dispersion[b]		15.26 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b]		1.7 mg
	Macrogol 6000		1.7 mg
	Glyceryl monostearate		1.0 mg
	Polysorbate 80		0.3 mg
	Citric acid		0.02 mg
	Pigment		0.02 mg
	Purified water[a]		70 μl
Enteric layer 2	Methacrylic acid copolymer dispersion[b]		84.0 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b]		9.33 mg
	Triethyl citrate		18.7 mg
	Glyceryl monostearate		6.0 mg
	Polysorbate 80		1.8 mg
	Citric acid		0.05 mg
	Pigment		0.12 mg
	Purified water[a]		142 μl
Enteric layer 3	Methacrylic acid copolymer dispersion[b]		7.63 mg
	Ethyl acrylate–methyl methacrylate copolymer dispersion[b]		0.85 mg
	Macrogol 6000		0.85 mg
	Glyceryl monostearate		0.50 mg
	Polysorbate 80		0.15 mg
	Citric acid		0.01 mg
	Pigment		0.01 mg
	Purified water[a]		35 μl
Overcoating layer	Mannitol		10.0 mg
	Purified water[a]		65 μl
		Total	270.0 mg

a) Removed during processing. b) Dry lacquer substance.

Table 3. Operating Conditions for Enteric-Coated Microgranules

	Active compound layer	Intermediate layer	Enteric layer	Overcoating layer
Total charge amount (kg)	2.55	3.3	3.12	3.24
Inlet air volume (m^3/min)	1.0	1.5	1.5	1.5
Inlet air temperature (°C)	55	75	75	75
Product temperature (°C)	ca. 30	ca. 40	ca. 40	ca. 40
Atomizing air volume (Nl/min)	80	100	100	100
Spray rate (g/min)	ca. 20	ca. 20	ca. 20	ca. 20
Rotor speed (rpm)	500	550	600	600

reported a new type of rapidly disintegrating tablet with good texture using microcrystalline cellulose with small particle size and spherical sugar granules. On the other hand, patients sense roughness when some water-insoluble excipient remains in powder form in the mouth after it absorbs saliva.

The rough texture was evaluated as more unpleasant in the order L-HPC>crospovidone>microcrystalline cellulose. The improvement of the rough texture of L-HPC was thus attempted from the viewpoint of water absorption properties. In this study, we selected the small particle sizes (mean particle size, approximately 23 μm) of L-HPC because they are smoother than large particle sizes (mean particle size, approximately 40 μm). There are three grades of L-HPC with different water absorption properties based on different hydroxypropoxy group content.[23] The water absorption properties of L-HPC were evaluated by viscosity measurement of L-HPC suspension. The viscosity decreased markedly with decreasing hydroxypropoxy group content, as shown in Fig. 1. It was thought that L-HPC with hydroxypropoxy group content lower than L-HPC-32 might decrease the water absorption capacity of L-HPC. A new grade of L-HPC (L-HPC-33), in which the hydroxypropoxy group content is

Table 4. Formulations of LFDT

Content of enteric-coated microgranules	37.5%	47.4%	64.3%
Enteric-coated microgranules	270.0 mg	270.0 mg	270.0 mg
Inactive granules			
Mannitol	102.0 mg	204.0 mg	306.0 mg
Low-substituted hydroxypropyl cellulose (L-HPC-33)[1]	15.0 mg	30.0 mg	45.0 mg
Microcrystalline cellulose	15.0 mg	30.0 mg	45.0 mg
Crospovidone	7.5 mg	15.0 mg	22.5 mg
Citric acid	1.5 mg	3.0 mg	4.5 mg
Aspartame	4.5 mg	9.0 mg	13.5 mg
Purified water[a]	22.5 μl	45 μl	67.5 μl
Flavor	1.5 mg	3.0 mg	4.5 mg
Magnesium stearate	3.0 mg	6.0 mg	9.0 mg
Total	420.0 mg	570.0 mg	720.0 mg

a) Removed during processing.

Table 5. Operating Conditions for Inactive Granules

Total charge amount (kg)	2.91
Inlet air volume (m³/min)	1.0
Inlet air temperature (°C)	65
Product temperature (°C)	ca. 25
Atomizing air volume (NL/min)	80
Spray rate (g/min)	ca. 20

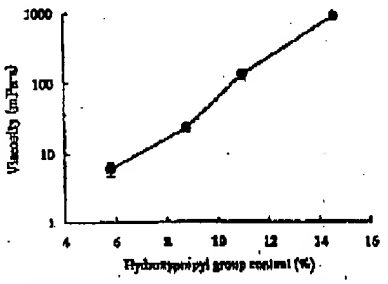


Fig. 1. Relationship between the Hydroxypropoxy Group Content of L-HPC and the Viscosity of the L-HPC Suspension

Data are expressed as mean±S.D. (n=3).

5.0—6.9, was developed in cooperation with Shin-Etsu Chemical Co., Ltd., and the L-HPC-33 suspension exhibited the lowest viscosity, as shown in Fig. 1. The data demonstrated that the capacity of water absorption of L-HPC-33 decreased as compared with other grades.

We also evaluated the rough texture by sensory evaluation and disintegration in the mouth using the tablets with the formulations shown in Table 1. The results are given in Table 6. The tablets comprised of L-HPC-32 and L-HPC-33 exhibited rapid disintegration in the mouth and those comprised of L-HPC-31 and L-HPC-30 did not disintegrate in the mouth. The data demonstrate that L-HPC-32 and L-HPC-33 with lower hydroxypropoxy group content are useful as the binder and disintegrant for tablets that disintegrate rapidly in the mouth. Only L-HPC-33 had a smooth texture. The others did not result in a proportional improvement of the rough texture with the decrease in the viscosity of L-HPC suspension because the water absorption capacity is too great compared to saliva secretion. The data suggest that a decrease in the water absorption properties of L-HPC and a decrease in the combined amount of water-insoluble excipients could improve the rough texture. Based on the results, L-HPC-33 with the lowest hydroxypropoxy group content was superior to the others in terms of roughness and disintegration in the mouth.

The effects of hydroxypropoxy group content in L-HPC on the qualities of tablets and rough texture of the rapidly disintegrating tablets containing enteric-coated microgranules were investigated. Tablets 360 mg in weight and 12 mm in diameter were prepared using a rotary tablet press at compression force of 25 kN/cm² and 30 rpm compression speed, as shown in Table 7. The tensile strength, disintegration time in the mouth, and roughness were evaluated, as shown in Table 7. The tensile strength of tablets comprised of L-HPC-33 was similar to that of tablets comprised of L-HPC-31. The disintegration time in the mouth of tablets comprised of L-HPC-33 was shorter than that of tablets comprised of L-HPC-31. The texture of tablets comprised of L-HPC-33 was smoother than that of tablets comprised of L-HPC-31. Based on these results, L-HPC-33 with the lowest hydroxypropoxy group content is the most suitable binder and disintegrant for LFDT.

Effect of Enteric-Coated Microgranule Content on Qualities of LFDT Various researchers have reported the effects of various excipients, particle size of coated pellets, coating level, and pellet content on drug release and crushing force in sustained-release formulations.[34—37] Beckert *et al.*[38] investigated the influence of compression force, excipients, pellet content, and coating formulation on the dissolved percentage in the acid stage and the disintegration time of rapidly disintegrating tablets containing enteric-coated pellets. They concluded that the dissolved percentage in the acid stage increased with the increasing content of enteric-coated pellets. Lehmann *et al.*[10] reported the effects of compression on dissolution behavior in the buffer stage after acid-resistance tests on tablets containing enteric-coated pellets.

In the development of LFDT, we aimed for sufficient tensile strength not to be damaged during ejection from the package, rapid disintegration in the mouth, and dissolution behavior in the acid and buffer stages similar to that of current tanaoprazole capsules. We set the desirable tensile strength at not less than 30 N/cm² and the desirable disintegration time in the mouth at not more than 30 s. To achieve these goals, it was necessary to determine the suitable enteric-coated microgranule content in LFDT. Three LFDTs

Table 6. Effects of Hydroxypropoxy Group Content in L-HPC on Sensory Evaluation

Hydroxypropoxy group content (grade)	Volunteer	5.8% (L-HPC-33)	8.9% (L-HPC-32)	11.0% (L-HPC-31)	14.6% (L-HPC-30)
Disintegration[a]	A	0	0	3	3
	B	0	0	3	3
	C	0	0	3	3
	D	1	1	3	3
	E	0	0	3	3
	F	0	0	3	3
	Mean	0.17	0.17	3	3
Rough texture[b]	A	0	2	2	2
	B	0	1	2	2
	C	0	2	2	2
	D	0	2	2	2
	E	0	2	2	2
	F	1	2	2	2
	Mean	0.17	1.83	2	2

a) 0, rapidly; 1, moderately; 2, slowly; 3, not disintegrated. b) 0, no roughness; 1, slight roughness; 2, rough.

Table 7. Formulation and Effect of Hydroxypropoxy Group Content in L-HPC on the Quality of LFDT

Hydroxypropoxy group content (grade)		5.8% (L-HPC-33)	11.0% (L-HPC-31)
Enteric-coated microgranules		135.0 mg	135.0 mg
Erythritol		181.5 mg	181.5 mg
Low-substituted hydroxypropyl cellulose		33.75 mg	33.75 mg
Microcrystalline cellulose		6.75 mg	6.75 mg
Citric acid		2.25 mg	2.25 mg
Magnesium stearate		0.75 mg	0.75 mg
	Total	360.0 mg	360.0 mg
Tensile strength[a]		48.3±2.0 N/cm^2	45.3±1.6 N/cm^2
Disintegration time in the mouth			
Volunteer A		22 s	46 s
B		35 s	63 s
C		33 s	61 s
D		30 s	52 s
E		24 s	48 s
F		28 s	56 s
Mean±S.D.		28.8±5.0 s	54.0±6.9 s
Sensory evaluation[b]			
Volunteer A		0	1
B		0	1
C		0	2
D		0	0
E		1	2
F		0	1
Mean		0.17	1.17

a) Data are expressed as mean±S.D. ($n=10$). b) 0, no roughness; 1, slight roughness; 2, rough.

were prepared by varying the content of enteric-coated microgranules, as shown in Table 6. The tensile strength, disintegration time in the mouth, and dissolution in the acid and buffer stages were evaluated, as shown in Table 8 and Fig. 2.

The tensile strength decreased and the disintegration time in the mouth was more rapid with the increase in the enteric-coated microgranule content in LFDT. The data demonstrate that a 47.4% content enteric-coated microgranules conferred the predetermined desirable qualities on LFDT.

The dissolved percentage in the acid stage increased and the dissolution in the buffer stage slightly decreased with the increase in the enteric-coated microgranule content in LFDT. The cleavage and crushing of the enteric layer occurred with the decrease in the combined amount of inactive granules that played a role in cushioning during compression. Since ethyl acrylate-methyl methacrylate copolymer dispersion and triethyl citrate have strong cohesion forces, the cohesion forces of the enteric-coated microgranules were enhanced with the decrease in the distance between the enteric-coated microgranules, and the enteric-coated microgranules delayed the disintegration of agglomerates during the dissolution test in the buffer stage with the increase in the enteric-coated microgranule content. The dissolved percentage of lansoprazole capsules in the acid stage was no more than 3% and the dissolution profiles of lansoprazole capsules in the buffer stage were similar to those of LFDT in which the content of the enteric-coated microgranules was set at 37.5% and 47.4%. Therefore 47.4% content of enteric-coated microgranules in LFDT was selected.

Effects of Compression Force on Qualities of LFDT LFDT with a 47.4% enteric-coated microgranule content were prepared by varying the compression force. The tensile

Table 8. Effects of Enteric-Coated Microgranule Content on the Qualities of LFDT

Enteric-coated microgranule content	37.5%	47.4%	64.3%
Tensile strength (N/cm²)	51.6±1.6	32.4±2.0	12.0±0.8
Disintegration time in the mouth (s)	49.2±9.6	26.8±6.7	9.7±2.0
Dissolved percentage in the acid stage (%)	0.4±0.1	2.5±0.5	11.0±0.6

Data are expressed as mean±S.D. (n=6).

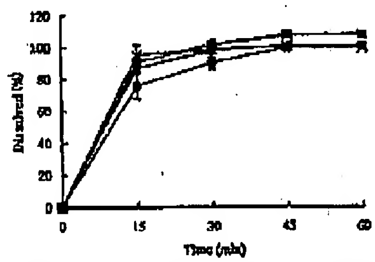


Fig. 2. Effect of Enteric-Coated Microgranule Content on Dissolution in the Buffer Stage

Data are expressed as mean±S.D. (n=6). ×, lansoprazole capsule. Enteric-coated microgranule content ■, 37.5%; ▲, 47.4%; ●, 64.3%.

Table 9. Effects of Compression Forces on the Qualities of LFDT

Compression force (kN/cm²)	20	25	30
Tensile strength (N/cm²)	25.3±0.3	34.2±0.6	41.8±0.7
Disintegration time in the mouth (s)	30.3±7.9	33.2±5.6	46.3±8.1
Dissolved percentage in the acid stage (%)	3.0±0.4	2.7±0.2	2.7±0.4

Data are expressed as mean±S.D. (n=6).

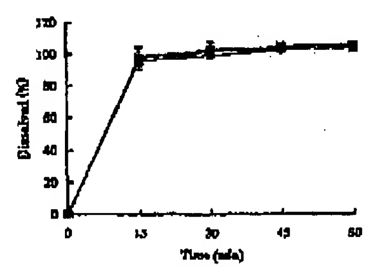


Fig. 3. Effect of Compression Forces on Dissolution in the Buffer Stage

Data are expressed as mean±S.D. (n=6). Compression force: ■, 20 kN/cm²; ▲, 25 kN/cm²; ●, 30 kN/cm².

strength, disintegration time in the mouth, and dissolution were evaluated, as shown in Table 9 and Fig. 3. The tensile strength increased and disintegration time in the mouth was slower with the increase in compression force. Compression force did not affect the dissolved percentage in the acid stage and dissolution profiles in the buffer stage. The data suggest that the enteric-coated microgranules have sufficient flexibility of the enteric layer and the inactive granules prevent enhancement of the cohesion forces of the enteric-coated microgranules.

Conclusions

To develop rapidly disintegrating tablets containing enteric-coated microgranules, methods to improve of the rough texture of the L-HPC used as a binder and disintegrant were examined. The new grade L-HPC-33 (hydroxypropyl group content, 5.0—6.9%) has no rough texture due to decreased water absorption. L-HPC-33 could thus be useful as a binder and disintegrant in rapidly disintegrating tablets.

The enteric-coated microgranule content in LFDT affected tensile strength, disintegration time in the mouth, and dissolution behavior in the acid and buffer stages. The desirable microgranule content of 47.5% was selected to achieve the desirable qualities of LFDT. Compression force affected tensile strength and disintegration time in the mouth, but did not affect dissolution behavior in the acid and buffer stages. The data suggest that the enteric-coated microgranules were not affected by impulsive force such as compression force with an appropriate enteric-coated microgranule content in LFDT.

Acknowledgments Appreciation is due to Mr. S. Sotake and Mr. T. Kashihara for their valuable suggestions in developing this formulation. Acknowledgments also go to Ms. T. Matsuda and Ms. Y. Fujishiro for assistance in performing assays.

References and Notes

1) Masaki K., Ban K., U.S. Patent 5466464 (1995).
2) Pebley W. S., Jager N. E., Thompson S. J., U.S. Patent 5298261 (1994).
3) Seager H., *J. Pharm. Pharmacol.*, 50, 375—382 (1998).
4) Corveleyn S., Remon J. P., *Int. J. Pharmaceut.*, 152, 215—225 (1997).
5) Corveleyn S., Remon J. P., *Int. J. Pharmaceut.*, 166, 65—74 (1997).
6) Corveleyn S., Remon J. P., *Int. J. Pharmaceut.*, 173, 149—155 (1998).
7) Corveleyn S., Remon J. P., *Drug Dev. Ind. Pharm.*, 25, 1005—1013 (1999).
8) Allen L. V., Wang B., U.S. Patent 5587180 (1996).
9) Allen L. V., Wang B., U.S. Patent 5595761 (1997).
10) Allen L. V., Wang B., Davies J. D., U.S. Patent 5635210 (1997).
11) Allen L. V., Wang B., Davies J. D., U.S. Patent 5807576 (1998).
12) Watanabe Y., Koizumi K., Zama Y., Kiriyama M., Matsumoto T., Matsumoto M., *Biol. Pharm. Bull.*, 18, 1308—1310 (1995).
13) Ishikawa T., Watanabe Y., Utoguchi N., Matsumoto M., *Chem. Pharm. Bull.*, 47, 1451—1454 (1999).
14) Ishikawa T., Mukai B., Shiraishi S., Fujii M., Matsumoto M., Watanabe Y., *Chem. Pharm. Bull.*, 48, 134—139 (2000).
15) Ishikawa T., Koizumi N., Mukai B., Utoguchi N., Fujii M., Matsumoto M., Endo H., Shirotake S., Watanabe Y., *Chem. Pharm. Bull.*, 49, 230—232 (2001).
16) Bi Y., Sunada H., Yonezawa Y., Danjo K., Otsuka A., Iida K., *Chem. Pharm. Bull.*, 44, 2121—2127 (1996).
17) Koizumi K., Watanabe Y., Morita K., Utoguchi N., Matsumoto M., *Int. J. Pharmaceut.*, 152, 127—131 (1997).
18) Mizumoto T., Masuda Y., Fukui M., U.S. Patent 5576014 (1996).
19) Kubo K., Oda K., Kaneko T., Satoh H., Nohara A., *Chem. Pharm. Bull.*, 38, 2853—2858 (1990).
20) Nagaya H., Satoh H., Maki Y., *J. Pharmacol. Exp. Ther.*, 248, 799—805 (1989).
21) Shimizu T., Nakano Y., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942—947 (2003).
22) Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1029—1035 (2003).
23) Brochure of Low-substituted Hydroxypropyl Cellulose prepared by Shin-Etsu Chemical Co., Ltd.
24) Prapaitrakul W., Whitworth C. W., *Drug. Dev. Ind. Pharm.*, 15, 2049—2053 (1989).
25) Bechard S. R., Leroux J. C., *Drug. Dev. Ind. Pharm.*, 18, 1927—1944 (1992).
26) Lopez-Rodriguez F. J., Torrado J. J., Torrado S., Escamilla C., Cadorniga R., Augsburger L. L., *Drug. Dev. Ind. Pharm.*, 19, 1369—1377 (1993).
27) Celik M., Maganti L., *Drug. Dev. Ind. Pharm.*, 20, 3151—3173

(1994).
28) Tortado J. J., Augsburger L. L., *Int. J. Pharmaceut.*, 106, 149—155 (1994).
29) Ayllon M. B., Dyer A. M., Khan K. A., *Drug. Dev. Ind. Pharm.*, 20, 3069—3104 (1994).
30) Becket T. E., Lehmann K., Schmidt P. C., *Int. J. Pharmaceut.*, 143, 13—23 (1996).
31) Lehmann K., Petereit H. U., Dreher D., *Drugs Made Germany*, 37, 53—60 (1994).

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

Edited by
Arthur H. Kibbe, Ph.D.
Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania

APhA
American Pharmaceutical Association
Washington, D.C.

PP
London, United Kingdom

Published by the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA
www.aphanet.org
and the Pharmaceutical Press
1 Lambeth High Street, London SE1 7JN, UK
www.pharmpress.com

First edition 1986
Second edition 1994
Third edition 2000

Printed in the United States of America

ISBN: 0-85369-381-1 (UK)
ISBN: 0-917330-96-X (USA)

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients / edited by Arthur H. Kibbe.—3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-917330-96-X
1. Excipients—Handbooks, manuals, etc. I. Kibbe, Arthur H. II. American Pharmaceutical Association.
[DNLM: 1. Excipients—Handbooks. QV 735 H236 2000]
RS201.E87 H36 2000
615'.19—dc21 99-044554

A catalogue record for this book is available from the British Library.

Managing Editor: Melanie Segala
Copyeditor: Paul Gardner
Indexer: Lillian Rodberg
Compositor: Roy Barnhill
Cover Designer: Tim Kempe

Contents

17. Pharmacopeias

China, Eur, Int, Jpn, and US.

18. Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hydroxypropyl methylcellulose.

19. Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

20. Specific References

1. Machida Y, Nagai T. Directly compressed tablets containing hydroxypropyl cellulose in addition to starch or lactose. *Chem Pharm Bull* 1974; 22: 2346–2351.
2. Delonca H, Joachim J, Mattha AG. Binding activity of hydroxypropyl cellulose (300 000 and 1 000 000 mol. wt.) and its effect on the physical characteristics of granules and tablets. *Farmaco (Prat)* 1977; 32: 157–171.
3. Delonca H, Joachim J, Mattha A. Effect of temperature on disintegration and dissolution time of tablets with a cellulose component as a binder [in French]. *J Pharm Belg* 1978; 33: 171–178.
4. Stafford JW, Pickard JF, Zink R. Temperature dependence of the disintegration times of compressed tablets containing hydroxypropylcellulose as binder. *J Pharm Pharmacol* 1978; 30: 1–5.
5. Kitamori N, Makino T. Improvement in pressure-dependent dissolution of trepibutone tablets by using intragranular disintegrants. *Drug Dev Ind Pharm* 1982; 8: 125–139.
6. Johnson JL, Holinej J, Williams MD. Influence of ionic strength on matrix integrity and drug release from hydroxypropyl cellulose compacts. *Int J Pharmaceutics* 1993; 90: 151–159.
7. Lindberg NO. Water vapour transmission through free films of hydroxypropyl cellulose. *Acta Pharm Suec* 1971; 8: 541–548.
8. Banker G, Peck G, Williams E, Taylor D, Pirakitikulr P. Evaluation of hydroxypropylcellulose and hydroxypropylmethylcellulose as aqueous based film coatings. *Drug Dev Ind Pharm* 1981; 7: 693–716.
9. Banker G, Peck G, Williams E, Taylor D, Pirakitikulr P. Microbiological considerations of polymer solutions used in aqueous film coating. *Drug Dev Ind Pharm* 1982; 8: 41–51.
10. Cohen EM, Grim WM, Harwood RJ, Mehta GN. Solid state ophthalmic medication. US Patent 4179497, 1979.
11. Harwood RJ, Schwartz JB. Drug release from compression molded films: preliminary studies with pilocarpine. *Drug Dev Ind Pharm* 1982; 8: 663–682.
12. Dumortier G, Zuber M, Chast F, Sandouk P, Chaumeil JC. Systemic absorption of morphine after ocular administration: evaluation of morphine salt insert in vitro and in vivo. *Int J Pharmaceutics* 1990; 59: 1–7.
13. Wirick MG. Study of the enzymic degradation of CMC and other cellulose ethers. *J Polymer Sci* 1968; 6(Part A-1): 1965–1974.
14. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose and cellulose gum. *J Am Coll Toxicol* 1986; 5(3): 1–60.
15. Schwartz BK, Clendenning WE. Allergic contact dermatitis from hydroxypropyl cellulose in a transdermal estradiol patch. *Contact Dermatitis* 1988; 18: 106–107.
16. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1990; No. 789.
17. Sweet DV, editor. Registry of Toxic Effects of Chemical Substances. Cincinnati: US Department of Health, 1987.

21. General References

Aqualon. Technical literature: *Klucel, hydroxypropyl cellulose, a nonionic water-soluble polymer, physical and chemical properties*, 1987.
Doelker E. Cellulose derivatives. *Adv Polymer Sci* 1993; 107: 199–265.
Ganz AJ. Thermoplastic food production. US Patent 3769029, 1973.
Klug ED. Some properties of water-soluble hydroxyalkyl celluloses and their derivatives. *J Polymer Sci* 1971; 36(Part C): 491–508.
Nippon Soda Co Ltd. Technical literature: *Nisso HPC*, 1993.
Opota O, Maillols H, Acquier R, Delonca H, Fortune R. Rheological behavior of aqueous solutions of hydroxypropylcellulose: influence of concentration and molecular mass [in French]. *Pharm Acta Helv* 1988; 63: 26–32.
Shin-Etsu Chemical Co Ltd. Technical literature: *L-HPC, low-substituted hydroxypropyl cellulose*, 1991.

22. Authors

RJ Harwood.

Hydroxypropyl Cellulose, Low-substituted

1. Nonproprietary Names

USP: Low-substituted hydroxypropyl cellulose

2. Synonyms

–

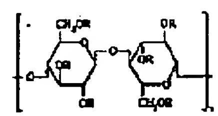
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [78214-41-2]

4. Empirical Formula

The USP describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. When dried at 105°C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups. Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades which have different particle sizes and substitution levels.

5. Structural Formula



Where R is H or $[-CH_2CH(CH_3)-O]_mH$ (M.S. = 0.1–0.4)

6. Functional Category

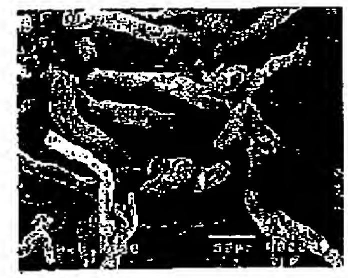
Tablet and capsule disintegrant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

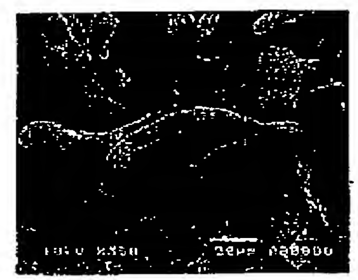
Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and also as a binder in wet granulation. There are a number of grades which have different particle sizes and substitution levels. *LH-11*, which has the medium substitution level and the largest particle size, is typically used as an anticapping agent and disintegrant for direct compression. *LH-21* is used as a binder and disintegrant for tablets through the wet-granulation process. Small particle grade *LH-31* is used especially for extrusion to produce granules as it has a small particle size which is better to pass a screen. Lower substitution grades *LH-22* and *LH-32* can be used when high binding strength is not necessary. If higher binding strength is needed, higher substitution grades *LH-20* and *LH-30* are also available.

Typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–25%.

SEM: 1
Excipient: Low-substituted hydroxypropyl cellulose, type *LH-11*
Manufacturer: Shin-Etsu
Magnification: 150x



SEM: 2
Excipient: Low-substituted hydroxypropyl cellulose, type *LH-21*
Manufacturer: Shin-Etsu
Magnification: 150x



8. Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor. It is tasteless.

SEM: 3
Excipient: Low-substituted hydroxypropyl cellulose, type LH-31
Manufacturer: Shin-Etsu
Magnification: 330×

9. Pharmacopeial Specifications

Test	USP
Identification	+
Chloride	≤0.36%
Heavy metals	≤0.001%
Arsenic	—
Loss on drying	≤5.0%
Residue on ignition	≤0.5%
Assay (of hydroxypropoxy groups)	5.0-16.0%

10. Typical Properties

Acidity/alkalinity: pH = 5.0-7.5 for 1% w/v aqueous suspension.
Angle of repose: see Table I.
Ash: 0.3-0.4%
Density (bulk): see Table I.
Density (tapped): see Table I.
Melting point: decomposition at 275°C.
Moisture content:
3% at 33% relative humidity;
31% at 95% relative humidity.
Specific gravity: 1.46
Solubility: practically insoluble in ethanol and in ether. Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble, but swells in water.

Table I: Typical properties for selected grades.

Grade	Hydroxypropyl content (%)	Density (bulk) (g/cm³)	Density (tapped) (g/cm³)	Average particle size* (μm)	Angle of repose (°)
LH-11	11	0.37	0.54	50	44
LH-21	11	0.36	0.62	40	41
LH-31	11	0.38	0.59	25	49
LH-22	8	0.36	0.52	40	45
LH-32	8	0.23	0.59	25	53
LH-20	13	0.34	0.62	40	45
LH-30	13	0.35	0.59	25	51

11. Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well-closed container.

12. Incompatibilities

Alkaline substances may interact. If a tablet formulation contains such a material, its disintegration may be extended after storage.

13. Method of Manufacture

Low-substituted hydroxypropyl cellulose is manufactured by reacting alkali cellulose with propylene oxide at elevated temperature. Following the reaction, the product is recrystallized by neutralization, washed, and milled.

14. Safety

Low substituted hydroxypropyl cellulose is generally regarded as a nontoxic and nonirritant material.

Animal toxicity studies showed no adverse effects in rats fed orally 6 g/kg/day over 6 months. No teratogenic effects were noted in rabbits and rats fed 5 g/kg/day.[1-4]

LD_{50} (rat, oral): > 15 g/kg[10]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided to minimize the risks of explosions.

16. Regulatory Status

Approved for use in pharmaceuticals in Japan, US, Europe, and other countries.

17. Pharmacopeias

US.

18. Related Substances

Hydroxypropyl cellulose.

19. Comments

—

20. Specific References

1. Kitagawa H, Yano H, Saito H, Fukuda Y. Acute, subacute and chronic toxicities of hydroxypropylcellulose of low-substitution in rats. *Pharmacometrics* 1976; 12: 41-66.
2. Kitagawa H, Saito H, Yokoshima T, Nabo T, Ushioda K, Ueda T, Oyabe S. Absorption, distribution, excretion and metabolism of C[14] hydroxypropylcellulose of low-substitution. *Pharmacometrics* 1976; 12: 33-39.
3. Kitagawa H, Satoh T, Saito H, Katoh M, Mukai T, Hashimoto Y. Teratological study of hydroxypropylcellulose of low substitution (L-HPC) in rabbits. *Pharmacometrics* 1978; 16: 259-269.
4. Kitagawa H, Saito H. General pharmacology of hydroxypropylcellulose of low substitution (L-HPC). *Pharmacometrics* 1978; 16: 299-302.

21. General References

Shin-Etsu Chemical Co Ltd. Technical literature: L-HPC, low-substituted hydroxypropyl cellulose, 1991.

22. Authors

RJ Harwood.

Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
Ainley Wade and Paul J Weller

American Pharmaceutical Association
Washington

The Pharmaceutical Press
London

1994

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral syrups and tablets, otic and topical preparations). Included in nonparenteral medicines licensed in the UK.

Hydroxyethyl cellulose is not currently approved for use in food products in Europe or the US although it is permitted for use in indirect applications such as packaging. This restriction is due to the high levels of ethylene glycol residues which are formed during the manufacturing process.

17. Pharmacopeias

Br, Eur, Fr, Ger, Gr, Hung, It, Neth, Port, Swiss and USPNF.

18. Related Substances

Ethylcellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose; Methylcellulose.

19. Comments

The limited scope for the use of hydroxyethyl cellulose in foodstuffs is in stark contrast to its widespread application as an excipient in oral pharmaceutical formulations.

20. Specific References

1. Gurny J, Durr M, Quint M-P, Plazonnet B. The effect of vehicle viscosity on the ocular bioavailability of L-653328. Int J Pharmaceutics 1990; 66: 23-28.
2. Cooper LI. Hydroxyethylcellulose gel as a dispersion vehicle. Am J Hosp Pharm 1984; 41: 1364-1702.
3. Delonca H, Joachim J, Mattha A. Influence of temperature on disintegration and dissolution time of tablets with a cellulose component as binder [in French]. J Pharm Belg 1978; 33: 171-178.
4. Kovács B, Merényi G. Evaluation of tack behavior of coating solutions. Drug Dev Ind Pharm 1990; 16: 2302-2323.
5. Wirick MG. Study of the substitution pattern of hydroxyethyl cellulose and its relationship to enzymic degradation. J Polymer Sci 1968; 6(Part A-1): 1705-1718.
6. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose and cellulose gum. J Am Coll Toxicol 1986; 5(3): 1-60.
7. Durand-Cavagna G, Delort P, Duprat P, Bailly Y, Plazonnet B, Gordon LR. Corneal toxicity studies in rabbits and dogs with hydroxyethyl cellulose and benzalkonium chloride. Fundam Appl Toxicol 1989; 13: 500-508.

21. General References

Amerchol Corp. Technical literature: Cellosize, hydroxyethyl cellulose, 1993.
Aqualon. Technical literature: Natrosol, hydroxyethyl cellulose, 1993.
Chauveau C, Maillols H, Delonca H. Natrosol 250 part I: characterization and modeling of rheological behavior [in French]. Pharm Acta Helv 1986; 61: 292-297.
Doelker E. Cellulose derivatives. Adv Polymer Sci 1993; 107: 199-265.
Hanger P, Tung MA, Runikis JO. Steady shear flow properties, rheological reproducibility and stability of aqueous hydroxyethylcellulose dispersions. Can J Pharm Sci 1976; 13: 4-7.
Klug ED. Some properties of water-soluble hydroxyalkyl celluloses and their derivatives. J Polymer Sci 1971; 36(Part C): 491-508.
Rufe RG. Cellulose polymers in cosmetics and toiletries. Cosmet Perfum 1975; 90(3): 93-94, 99-100.

22. Authors

USA: RJ Harwood, JL Johnson.

Hydroxypropyl Cellulose

1. Nonproprietary Names

BP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2. Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel; Methocel; Nisso HPC*; oxypropylated cellulose.

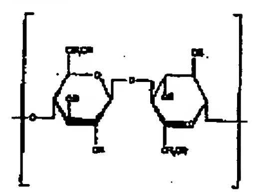
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Empirical Formula Molecular Weight

The USPNF XVII describes hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades which have different solution viscosities. Molecular weight ranges from 50 000-1 250 000, see also Section 10.

5. Structural Formula



Where R is H or $[-CH_2-CH(CH_3)-O]_mH$

6. Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended release matrix former. Concentrations of between 2-6% w/w of hydroxypropyl cellulose may be used as a binder in either wet granulation or dry, direct compression tableting processes.[1-5] Concentrations of between 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[6] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the hydroxypropyl cellulose viscosity and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Either aqueous solutions, containing hydroxypropyl cellulose along with some methylcellulose, or ethanolic solutions may be used.[7-9] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, see Section 18.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[10-12]

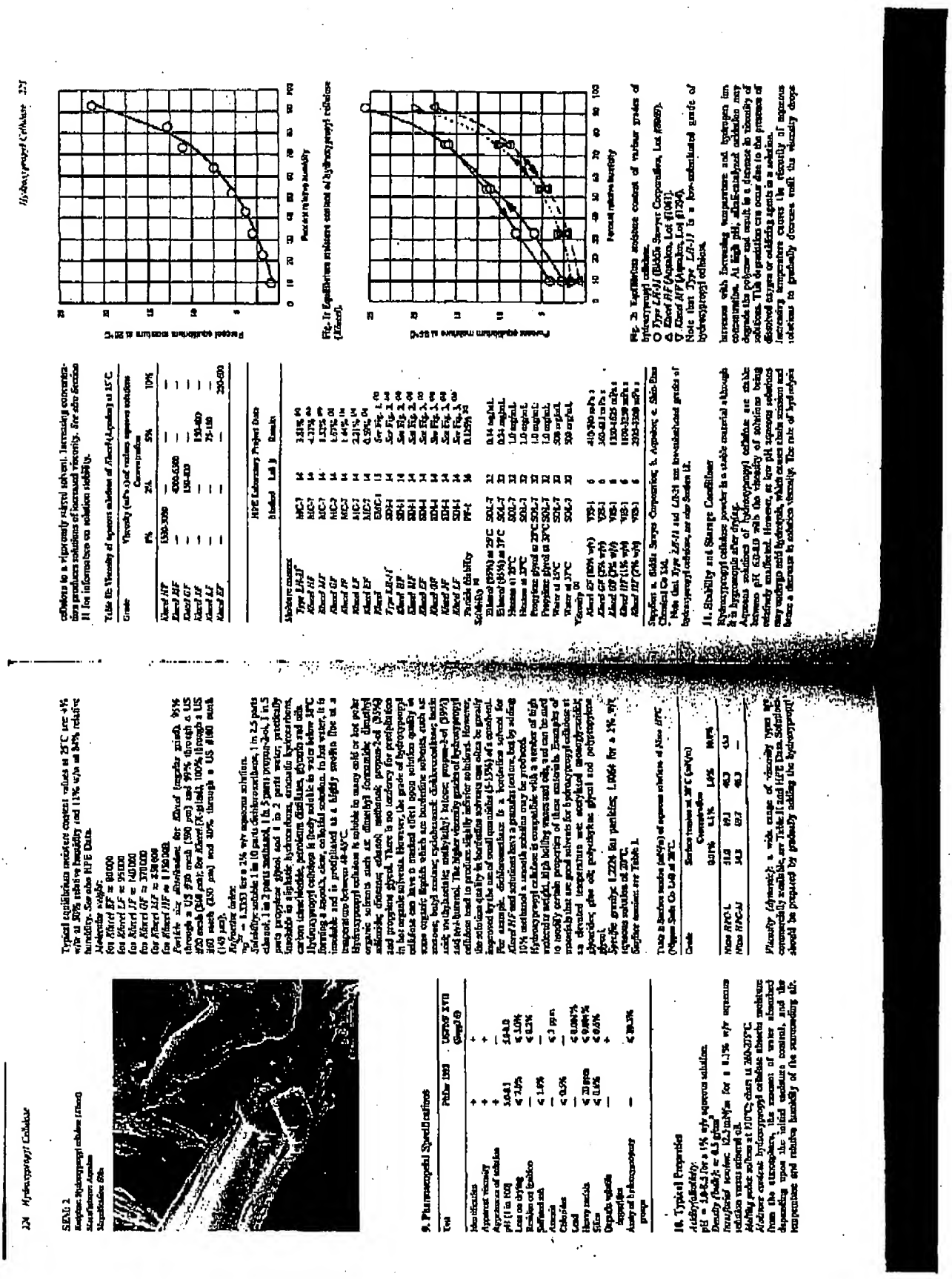
Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Use	Concentration (%)
Extended release matrix former	15-35
Tablet binder	2-6
Tablet film coating	5

8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. See also Sections 4 and 5.

SEM: 1
Excipient: Hydroxypropyl cellulose (Klucel)
Manufacturer: Aqualon
Magnification: 60x



committee on food additives. Tech Rep Ser Wld Hlth Org 1990; No. 789.

17. Sweet DV, editor. Registry of toxic effects of chemical substances. Cincinnati: US Department of Health, 1987.

18. Kawashima Y, Takeuchi H, Hino T, Niwa T, Lin T-L, Sekigawa F, Kawahara K. Low-substituted hydroxypropylcellulose as a sustained-drug release matrix base or disintegrant depending on its particle size and loading in formulation. Pharm Res 1993; 10: 351-355.

19. Kleinebudde P. Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets using extrusion/spheronization. Int J Pharmaceutics 1993; 96: 119-128.

21. General References

Aqualon. Technical literature: Klucel hydroxypropyl cellulose, a nonionic water-soluble polymer, physical and chemical properties, 1987.

Doelker E. Cellulose derivatives. Adv Polymer Sci 1993; 107: 199-265.

Ganz AJ. Thermoplastic food production. US Patent 3769029, 1973.

Klug ED. Some properties of water-soluble hydroxyalkyl celluloses and their derivatives. J Polymer Sci 1971; 36(Part C): 491-508.

Nippon Soda Co Ltd. Technical literature: Nisso HPC, 1991.

Ojeda O, Mallols H, Acquier R, Delonca H, Fortune R. Rheological behavior of aqueous solutions of hydroxypropylcellulose: influence of concentration and molecular mass [in French]. Pharm Acta Helv 1988; 63: 16-22.

Shin-Etsu Chemical Co Ltd. Technical literature: L-HPC, low-substituted hydroxypropyl cellulose, 1991.

22. Authors

USA: RJ Harwood, JL Johnson.

Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

Cellulose, hydroxypropyl methyl ether; *Culminal MHPC*; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*.

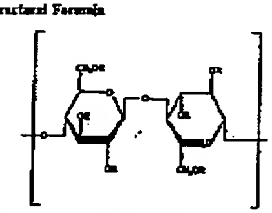
3. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether
[9004-65-3]

4. Empirical Formula Molecular Weight

The PhEur 1992 describes hydroxypropyl methylcellulose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hydroxypropyl methylcellulose defined in the USP XXII specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

6. Functional Category

Coating agent; film-former; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder,[1] in film-coating[2-7] and as an extended release tablet matrix.[8-12] Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix.

Depending upon the viscosity grade, concentrations between 2-10% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hydroxypropyl methylcellulose is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

9. Pharmacopeial Specifications

Test	PhEur 1992	USP XXII (Suppl 2)
Identification	+	+
Appearance of solution	+	—
pH (1% w/w solution)	5.5-8.0	—
Apparent viscosity	+	+
Loss on drying	≤ 10.0%	≤ 5.0%
Residue on ignition		
for viscosity grade > 50 mPa s	—	≤ 1.5%
for viscosity grade ≤ 50 mPa s	—	≤ 3.0%
for type 1828 of all viscosities	—	≤ 5.0%
Sulfated ash	≤ 1.0%	—
Arsenic	—	≤ 2 ppm
Chlorides	≤ 0.5%	—
Heavy metals	≤ 20 ppm	≤ 0.001%
Methoxy content		
Type 1828	—	16.5-20.0%
Type 2208	—	19.0-24.0%
Type 2906	—	27.0-30.0%
Type 2910	—	28.0-30.0%
Hydroxypropoxy content		
Type 1828	—	23.0-32.0%
Type 2208	—	4.0-12.0%
Type 2906	—	4.0-7.5%
Type 2910	—	7.0-12.0%

10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/w aqueous solution.